REMARKS

Claims 1-38 are cancelled. Claims 39-48 are added and now active in this application.

The present invention relates to a method of treating tumors associated with a hyperactivation of the signaling pathway of the Hedgehog protein, which tumors are medulloblastomas, glioblastomas, oligodendrogliomas, basal cell carcinoma, trichoepithelioma, rhabdomyosarcoma and tumors of the kidney.

Claims 16-25, 27-33 and 38 stand rejected under 35 U.S.C. 102(b) as being anticipated by Haak et al.

However, this reference fails to either disclose or suggest the claimed invention.

Haak et al. merely describe the use of a progesterone antagonist, mifepristone, for the treatment of meningioma. Meningioma are progesterone dependant tumors. Clearly, this reference would have neither disclosed nor suggested the claimed invention to one skilled in the art.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Claims 16-25, 27-31, 34 and 38 stand rejected under U.S.C. 102(b) as being anticipated by Reiner et al. (WO 1998/48784).

W0 98/48784 (Reiner) merely describes the use of RU486 (mifepristone) for inhibiting amyloidosis in disorders in which amyloid deposition occurs such as Alzheimer's disease, stroke and head trauma. This reference merely describes RU486 is described as an ABC transporter blocker. This reference would have neither disclosed nor suggested the claimed invention to one skilled in the art.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Claims 16-25, 27-31 and 35 stand rejected under 35 U.S.C. 102(b) as being anticipated by Gettys et al.

Gettys et al. merely describe the use of mifepristone acting as a glucocorticoid antagonist for the treatment of diabetes.

In contrast, the present invention provides inhibitors of the Hedgehog protein signaling pathway which are not toxic for humans.

Further the present inventors have surprisingly discovered that mifepristone inhibits the Hedgehog protein signaling pathway. This is quite unexpected for the reasons mentioned below.

First, figures 1 and 2 of example 1 of the present specification show that mifepristone inhibits this pathway. This observation is specific to Hedgehog protein signaling pathway and independent of progesterone and glucocorticoid inhibitor properties of mifepristone, thus, clearly distinguishing the claimed invention from Haak et al and Gettys et al, respectively.

In addition to this example, attached to this Amendment is a Rule 132 Declaration describing tests demonstrating the effect of mifepristone on the activity of the Hedgehog signaling pathway in neural progenitor cells, precursors of brain tumors.

The Declaration clearly demonstrates that mifepristone induces a decrease in the number of proliferating cells in the two main areas of neurogenesis in the adult brain, the sub-ventricular zone (ZSV) of lateral ventricles and the subgranular zone (ZSG) in the hippocampus.

These results demonstrates that mifepristone shows the same behavior as the first molecule described as an Smo receptor antagonist of the Hedgehog protein signaling pathway, cyclopamine (Palma et al., Development, 2005, Lai et al., Nat Neurosci, 2003, see attached articles).

In addition, several studies have reported that increases in corticosterone inhibit neurogenesis in the hippocampus (Gould et al. J. Neurosci., 1992, 12 (9): 3642-3650; Stranahan et al. Nat. Neurosci., 2008, 11 (3): 309-317, see attached articles). More recently, Lau et al. have reported that corticosteroids also reduce cell proliferation in the ZSV (Lau et al. Restaur. Neurol. Neurosci., 2007,25: 17-23).

To the contrary, one skilled in the art would have expected that mifepristone, which is known as a glucocorticoid receptors antagonist, would lead to an increase in the number of proliferating

cells in the ZSG and ZSV (i.e. the opposite effect of those observed with a corticosteroid), and not to the decrease observed in the present results.

These results thus indicate that mifepristone exhibits a totally unexpected effect compared to knowledge of the state of the art: its effect on neural progenitor is similar to a corticosteroid hormone when it is an antagonist of corticosteroids.

These results demonstrate that mifepristone does not act on neural progenitors via the glucocorticoid receptors and also confirm that mifepristone has the ability to inhibit the proliferation of neural progenitors via the Hedgehog protein signaling pathway.

The neural progenitors have a broad potential for differentiation. Clarke et al.'s review (Science, 2000, 288: 1666-1663) describes the ability of adult neural progenitor cells to differentiate into muscle cells (page 1661, left column, lines 23-25), in cells of mesonephric tubules (page 1661, middle column, line 10) and epidermal cells (page 1661, middle column, line 11) (see also Table 1, page 1663); all of these cells, therefore, share the common characteristic of having a proliferation regulated by the Hedgehog signaling pathway.

Thus, tumors associated with a hyperactivation of the Hedgehog proteins signaling pathway of brain cells (medullob~astomas, glioblastomas, oligodendrogliomas), muscle cells (rhabdomyosarcoma), skin cells (basal cell carcinoma, trichoepithelioma) and kidney cells (renal tumors) will exhibit a behavior identical to that of neural progenitors in the presence of mifepristone: mifepristone will be able to inhibit their proliferation.

These data confirm the inhibitory effect of mifepristone on cell proliferation via the hyperactivation of the Hedgehog protein signaling pathway; which is consistent with the results obtained in the in vitro differentiation of the C3HlOT112 cell line described in Example 1 of the present specification.

Clearly, it is emphasized again that the use of mifepristone for the treatment of tumors associated with a hyperactivation of the signaling pathway of the Hedgehog protein chosen among medulloblastomas, glioblastomas, oligodendrogliomas, the basal cell carcinoma, trichoepithelioma, rhabdomyosarcoma and tumors of the kidney, would not – and could not have

been obvious from Haak et al., Reiner et al. nor Gettys et al. which describe mifepristone as a progesterone antagonist, a ABC transporter blocker and a glucocorticoid antagonist, respectively.

Notably, these references disclose that mifepristone is effective **only** in the treatment of tumors whose growth is dependent on progesterone or glucocorticoids. Hence, the skilled person would have been deterred from using mifepristone to treat other tumors whose growth is linked to a hyperactivation of the Hedgehog protein signaling pathway, for example, that involves neither the progesterone receptor nor glucocorticoid.

Thus in view of all of the above, it is clear that none of the references of record, either alone or in combination with the others, would have disclosed or suggested the claimed invention to one skilled in the art at the time it was made.

Further, even assuming, *arguendo*, that the claimed invention would have been obvious to are skilled in the art at the time it was made, the attached Declaration clearly rebuts any such presumption of obviousness for the reasons noted above.

Hence, this ground of rejection - as well as the previously noted grounds of rejection – are unsustainable and should be withdrawn.

Claim 28 stands rejected under 35 USC 112, second paragraph.

However, in view of the above claim amendments, this ground of rejection is deemed moot.

Claim 27 stands objected to under 37 CFR 1.75(c).

However, in view of the above claim amendments, this ground of rejection is deemed moot.

Accordingly, in view of all of the above claim amendments and attendant remarks, it is believed that this application now stands in condition for allowance.

Favorable consideration and early notice to this effect is earnestly solicited.

Respectfully submitted,
THE NATH LAW GROUP

William E. Beaumont
Registration No. 30,996
Customer No. 20529

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THE NATH LAW GROUP
112 S. West Street
Alexandria, Virginia 22314
Tel: (703) 548-6284
Fax: (703) 683-8396
WEB/tld